Communication

Organocatalytic Enantioselective Formal C(sp2)-H Alkylation

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Organocatalytic Enantioselective Formal C(sp^2)–H Alkylation

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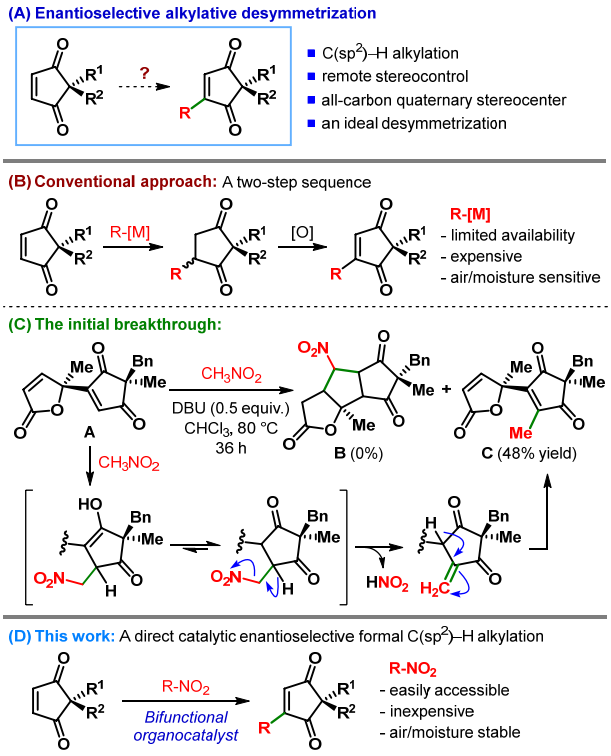
Supporting Information Placeholder

ABSTRACT: An organocatalytic enantioselective formal C(sp^2)–H alkylation is reported. This alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-dione is catalyzed by a bifunctional tertiary aminourea derivative, utilizes air-stable and inexpensive nitroalkanes as the alkylating agents, and delivers synthetically versatile five-membered carbocycles containing an all-carbon quaternary stereogenic center remote from the reaction site in excellent enantioselectivity.

The importance of chiral cyclopentanes as synthetically useful building blocks and common structural motifs of complex targets has stimulated considerable research activities on their enantioselective synthesis.[1] Among various methods for accessing these enantioenriched carbocyclic frameworks, desymmetrization of prochiral or *meso* compounds through catalytic enantioselective transformations represents a powerful strategy.[2] The biggest advantage of such asymmetric desymmetrization reactions lies in their ability in controlling stereochemistry remote from the reaction site. This aspect becomes particularly prominent for the creation of all-carbon quaternary stereogenic centers.

Inspired by the wide abundance of five-membered carbocyclic frameworks in bioactive natural products[3] and the challenges in the enantioselective generation of all-carbon quaternary stereogenic centers,[4] we have recently developed a highly efficient desymmetrization protocol for 2,2-disubstituted cyclopentene-1,3-diones through a direct vinylogous nucleophilic addition of deconjugated butenolides.[5] This reaction delivers densely functionalized products containing three stereogenic centers with excellent diastereo- and enantioselectivity. The construction of multiple stereocenters through a single operation bears its own advantage in creating stereochemical diversity. However, a desymmetrization reaction, in its strict sense, should proceed without the creation of any additional stereocenter and should result in the minimum variation of the existing functionalities. Pursuing our interest along this direction, we sought an alkylative desymmetrization reaction of prochiral cyclopentene-1,3-diones (Scheme 1A). Such a C(sp^2)–H alkylation would not only create an all-carbon quaternary stereogenic center remote from the reaction site, but would also represent an ideal desymmetrization. This type of reactions is conventionally carried out using a two-step sequence consisting of an asymmetric conjugate addition of a metalloalkyl or equivalent species followed by oxidation (Scheme 1B).[6] To this end, the highly diastereo- and enantioselective Cu-catalyzed addition of metalloalkyl reagents to cyclopentene-1,3-diones, developed by Mikami and co-workers is particularly noteworthy.[2c] Despite immense popularity of this strategy, a prominent drawback lies in the limited accessibility and relatively high cost of the organometallic alkyl source, besides demanding reaction conditions.

Scheme 1. Catalytic Enantioselective Alkylative Desymmetrization of Cyclopentene-1,3-diones



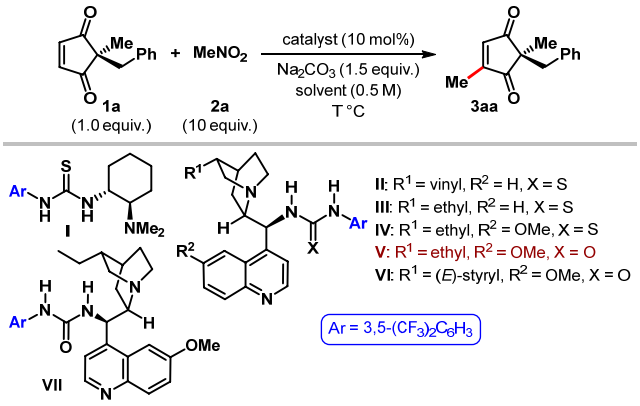
We became interested in a direct and step-economic enantioselective alkylative desymmetrization of prochiral cyclopentene-1,3-diones using an easily accessible, inexpensive and air-stable alkyl source. The initial breakthrough towards finding such an alkylating agent emerged as the fortunate consequence of our futile attempt to facilitate a double Michael reaction of **A** for generating a tricyclic compound **B** (Scheme 1C). Using nitromethane as the nucleophile, this base-mediated reaction, instead produced a methylated analog **C** as an equimolar mixture of two atropisomers.[7] This formal C(sp^2)–H methylation reaction presumably proceeds via an addition-elimination-isomerization pathway (Scheme 1C). Despite their growing application in enantioselective synthesis,[8] nitroalkanes, to the best of our knowledge, have never been used as an alkyl source. This is particularly surprising since the propensity of nitro as a leaving group is well documented in the literature.[9]

Encouraged by this unexpected findings and considering the easy accessibility and stability of a wide range of nitroalkanes, we

embarked into applying this concept for the enantioselective alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones (Scheme 1D). The results of this successful enantioselective formal C(sp^2)–H alkylation are presented through this communication.

Our initial task was to identify a suitable catalyst system. We reasoned that an enantiogroup-differentiating conjugate addition (of nitroalkane or the corresponding nitronate) to cyclopentene-1,3-diones is necessary to transform the prochiral center into an all-carbon quaternary stereogenic center. Tertiary amino-(thio)urea based bifunctional compounds were chosen as the catalyst candidate to accomplish this task, given their widespread precedence in activating nitroalkanes for various enantioselective transformations.[10]

Table 1. Catalyst Evaluation and Reaction Optimization



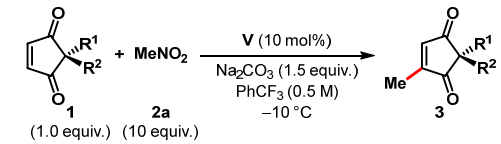
entry	cat.	solvent	temp (°C)	time (h)	conv. (%)[a]	er[b]
1	-	$CHCl_3$	25	24	<5	-
2	**I**	$CHCl_3$	25	20	>95	20:80
3	**II**	$CHCl_3$	25	15	>95	81.5:18.5
4	**III**	$CHCl_3$	25	36	>95	86:14
5	**IV**	$CHCl_3$	25	20	>95	88:12
6	**IV**	$PhCF_3$	25	12	>95	90:10
7	**IV**	$PhCF_3$	0	40	>95	94:6
8	**IV**	$PhCF_3$	−10	55	>95	95:5
9[c]	**IV**	$PhCF_3$	−10	72	85	95:5
10	**V**	$PhCF_3$	−10	48	>95 (88)[d]	97:3
11	**VI**	$PhCF_3$	−10	48	>95	94.5:5.5
12	**V**	$PhCF_3$	−20	72	>95	97.5:2.5
13	**VII**	$PhCF_3$	−10	48	>95 (84)[d]	6:94

[a]Conversion of **1a** as determined by ^{1}H NMR of the crude reaction mixture. [b]Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase. [c]Using 5.0 equiv. nitromethane (**2a**). [d]Values in parentheses represent isolated yield after column chromatography.

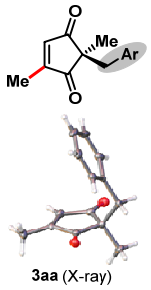
An important issue had to be resolved at the outset of this investigation: an equimolar amount of external base is necessary for quenching the nitrous acid byproduct (see Scheme 1C) to prevent catalyst poisoning. However, this external (achiral) base must not catalyze the (non-selective) conjugate addition on its own.

It is against this backdrop, we began our studies with prochiral 2-benzyl-2-methylcyclopent-4-ene-1,3-dione **1a** as the test substrate and nitromethane (**2a**) as the alkylating agent (Table 1). A survey of a small collection of bases[7] revealed Na_2CO_3 to be the suitable external base as no product formation could be detected in the presence of 1.5 equiv. of Na_2CO_3 alone, when the reaction was conducted in $CHCl_3$ at 25 °C (Table 1, entry 1). However, the combination of 10 mol% of the Takemoto catalyst[11] (**I**) and 1.5 equiv. of Na_2CO_3 resulted in complete conversion of **1a** within 20 h and furnished the desired product **3aa** with 20:80 er (Table 1, entry 2). Encouraged by this moderate yet promising level of enantioselectivity, a number of similar bifunctional catalysts were evaluated.[7] Cinchona alkaloid-derived thioureas were proved to be good catalyst candidates (entries 3-5), particularly dihydroquinine derived thiourea **IV**, which increased the enantioselectivity to 88:12 er (entry 5). Reaction medium offered some assistance[7] and the best results were obtained in trifluorotoluene ($PhCF_3$), both in terms of the enantioselectivity and the reaction rate (entry 6). The latter factor allowed us to reduce the reaction temperature down to −10 °C, when the product was obtained with 95:5 er (entry 8). Reduction in the amount of nitromethane did not affect the enantioselectivity, although the reaction rate was decreased significantly (entry 9). The urea derivative **V** was found to be even more efficient (entry 8 vs 10) and the dihydro-cinchona derivatives were generally found to be superior compared to their dehydro analogs.[7] We have also tested the corresponding (*E*)-styryl derivative **VI**, without any beneficial effect (entry 11). Further improvement in er is possible by carrying out the reaction at −20 °C, albeit at the expense of reaction rate (entry 12). Considering the practicality, −10 °C was chosen as the working temperature for the subsequent studies. We were pleased to find that the other product antipode (*ent*-**3aa**) could be accessed with a reasonably

Table 2. Scope of the Desymmetrization with respect to Cyclopentene-1,3-dione[a,b,c]

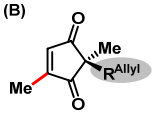


(A)



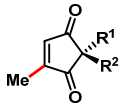
Ar	*t* [h]	yield [%]	er
Ph (**3aa**)	48	88	97:3 (99.6:0.4)[d]
(**3ba**)	48	85	96.5:3.5
4-MeC_6H_4 (**3ca**)	48	83	96.5:3.5
2-MeC_6H_4 (**3da**)	48	79	94:6
1-naphth (**3ea**)	60	83	97:3
2-naphth (**3fa**)	48	90	97:3
4-ClC_6H_4 (**3ga**)	48	84	94:6
3-ClC_6H_4 (**3ha**)	48	88	95:5
2-ClC_6H_4 (**3ia**)	70	80	87:13
4-BrC_6H_4 (**3ja**)	48	82	93.5:6.5

(B)



R^{Allyl} = **3ka**: 72 h, 84% yield, 92:8 er; **3la**: 72 h, 73% yield, 97.5:2.5 er

(C)



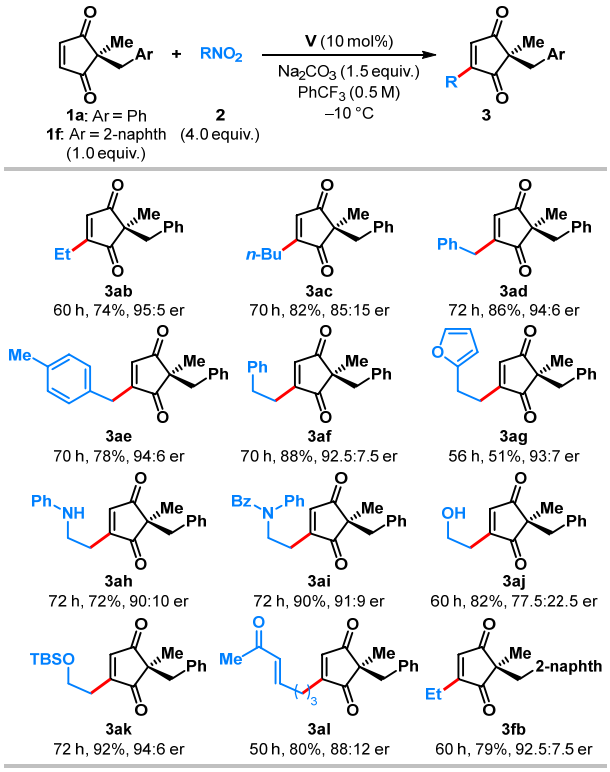
R^1	R^2	*t* [h]	yield [%]	er
Me	*i*-Bu (**3ma**)	72	78	90:10
Me	CH_2OTBS (**3na**)	72	82	96:4
Me	Ph (**3oa**)	48	90	83.5:16.5
Me	$CHPh_2$ (**3pa**)	70	86	98:2
Me	$CH(4\text{-}ClC_6H_4)_2$ (**3qa**)	48	83	98:2
Et	$CHPh_2$ (**3ra**)	70	90	94:6[e]

[a]Reactions were carried out on a 0.1 mmol scale. [b]Yields correspond to the isolated yield. [c]Er was determined by HPLC analysis on a chiral stationary phase. [d]Value in parenthesis indicates the er after a single recrystallization. [e]Reaction was performed at 0 °C.

high er using the corresponding pseudoenantiomeric catalyst **VII** under the optimized reaction conditions (entry 13).

With the optimum catalyst identified and the reaction conditions established (Table 1, entry 10), the generality of this alkylative desymmetrization reaction was explored. We initially focused on elucidating the scope of cyclopentene-1,3-diones towards methylation using nitromethane (**2a**). As revealed in table 2, a wide range of 2,2-disubstituted cyclopentene-1,3-diones having different substitution pattern at the quaternary center underwent facile methylative desymmetrization under our optimized reaction conditions. The substrates having the combination of a methyl, and various sterically and electronically tuned benzylic substituents were found to be the most suitable, and furnished the alkylated products (**3aa**–**ja**) uniformly in high yield and with good to excellent er in most cases (Table 2A). As exemplified with **3aa**, essentially enantiopure product could be obtained after a single recrystallization. The single crystal X-ray analysis of **3aa** revealed the absolute configuration of our products,[12] which was confirmed by synthetic transformation to the known compounds (see Scheme 2A). The scope is not limited to benzylic substituents as similar level of enantioselectivity was maintained with other cyclopentene-1,3-diones containing allylic (Table 2B), alkyl and benzhydrylic substituents at the quaternary stereocenter (Table 2C). Notably lower enantioselectivity observed in the case of 2-chlorobenzyl (**3ia**) and phenyl-substituted diones (**3oa**) points out the current limitation of our protocol. The combination of ethyl and benzhydryl substrate was also studied: the corresponding methylated product (**3ra**) was obtained with lower er (cf. **3pa**) as the reaction had to be conducted at 0 °C to achieve a reasonable reaction rate.

Table 3. Scope of the Desymmetrization with regard to Nitroalkane[a,b,c]

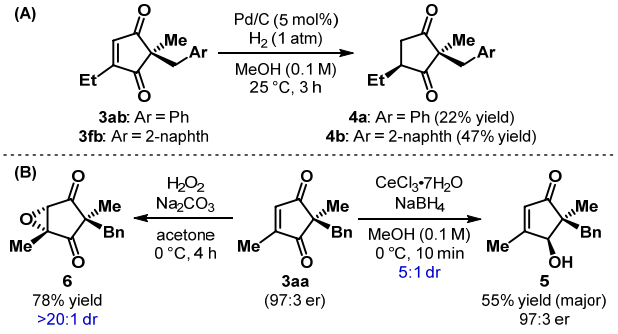


[a]Reactions were carried out on a 0.1 mmol scale. [b]Yields correspond to the isolated yield. [c]Er was determined by HPLC analysis on a chiral stationary phase.

After achieving the formal enantioselective C(sp^2)–H methylation with various 2,2-disubstituted cyclopentene-1,3-diones, we turned our attention to alkylations using other nitroalkanes. The results are summarized in Table 3. In this case only 4.0 equivalent of nitroalkane was sufficient to reach a reasonable reaction rate. Simple alkyl (**3ab-ac, 3fb**), benzylic (**3ad-ae**) as well as homobenzylic groups (**3af-ag**) were smoothly introduced in moderate to good yield and in most cases with high er. Functionalized nitroalkanes containing amine (**2h**), amide (**2i**), alcohol (**2j**) and α,β-unsaturated ketone (**2l**) could also be employed. Although the products containing amine and amide functionalized alkyl groups (**3ah-ai**) could be obtained with acceptable er, drastically reduced enantioselectivities were observed in the case of 2-hydroxyethyl (**3aj**) and 4-heptenone (**3al**). However, the TBS-protected 2-hydroxyethyl group could be introduced with good enantioselectivity (**3ak**).

Having successfully developed a formal enantioselective C(sp^2)-H alkylation, we directed our efforts to demonstrate the synthetic utility of the resulting desymmetrized cyclopentene-1,3-diones. Hydrogenation under Pd-catalysis proved to be completely diastereoselective, as illustrated by two examples (Scheme 2A). The low yields of **4a-b** are due to the formation of considerable amount of the corresponding debenzylated products under the reaction conditions. The relative and absolute stereochemistry of **4a-b** have previously been confirmed by Mikami et al.[2c] and in turn established the absolute configuration of our alkylated products. Reaction under Luche condition surprisingly led to the regioselective reduction of the more hindered keto group of **3aa**, even though the reaction was found to be only moderately diastereoselective (5:1 dr). However, the diastereomerically pure alcohol **5** could be isolated in 55% yield after chromatographic purification without any erosion of er (Scheme 2B). Weitz-Scheffer-type epoxidation[13] of **3aa**, on the other hand, furnished **6** as a single diastereomer in 78% yield (Scheme 2B).

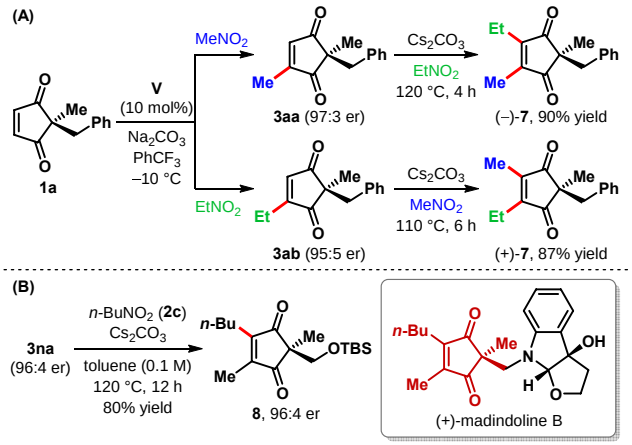
Scheme 2. Synthetic Transformations of the Desymmetrized Adducts



In addition to the synthetic transformations discussed above, the alkylated products were subjected to a second alkylation with a different nitroalkane (Scheme 3). Using Cs_2CO_3 as the base, these reactions required somewhat demanding conditions, but the products containing unsymmetrical tetrasubstituted olefins were obtained in excellent yield. For example, the methylated adduct **3aa** upon reaction with nitroethane furnished (–)-**7** in 90% yield. More importantly, by simply reversing the sequence of nitroalkanes, the other product enantiomer can be accessed under the influence of the same catalyst enantiomer: the ethylated adduct **3ab** on treatment with nitromethane produced (+)-**7** in 87% yield (Scheme 3A). As a brief demonstration of the applicability of this double alkylation protocol, we have synthesized the core structure

(**8**) of antibiotic natural product (+)-madindoline B[14] in a single step from one of our desymmetrized products, **3na** (Scheme 3B). Thus, treatment of **3na** with nitrobutane (**2c**) and Cs_2CO_3 under refluxing toluene provided **8** in high yield after 12 h without compromising its stereochemical integrity. The stereoisomeric natural product, madindoline A, can in principle be obtained similarly by changing the sequence of nitrobutane and nitromethane.

Scheme 3. Double Alkylation and the Synthesis of the Core Structure of Madindolines



Overall, we have developed an enantioselective alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones catalyzed by a dihydroquinine-based bifunctional urea derivative. Using easily accessible, inexpensive and air-stable nitroalkanes as the alkylating agent, this formal C(sp^2)-H alkylation represents a near-ideal desymmetrization and delivers products containing an all-carbon quaternary stereogenic center in good to excellent yields and with high enantioselectivities. The mild reaction conditions allow for the introduction of various functionalized alkyl groups. The possibility of a second alkylation and its applications has also been demonstrated. This report, to our knowledge, is the first example of the use of nitroalkanes as the alkylating agent. We expect these findings to be of broader consequences and applicable to other alkylative and related transformations. Investigations along these lines are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, HPLC traces and crystallographic data for **3aa** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(12) CCDC 1034440 contains the crystallographic data for **3aa** (also available as Supporting Information). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

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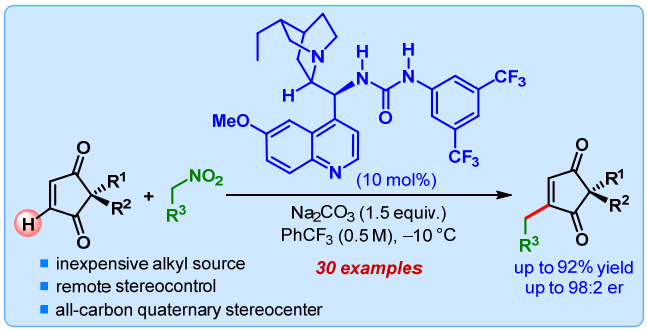
TOC Graphic


MeO
CF3
CF3
(10 mol%)
Na2CO3 (1.5 equiv.)
PhCF3 (0.5 M), –10 °C
30 examples
inexpensive alkyl source
remote stereocontrol
all-carbon quaternary stereocenter
up to 92% yield
up to 98:2 er